



US009006289B2

(12) **United States Patent**  
**Jiang et al.**

(10) **Patent No.:** US 9,006,289 B2  
(45) **Date of Patent:** Apr. 14, 2015

(54) **LEVOTHYROXINE FORMULATIONS**

(75) Inventors: **Zhi-Qiang Jiang**, Skokie, IL (US);  
**Arunya Usayapant**, Mundelein, IL (US); **George Monen**, Woodridge, IL (US)

(73) Assignee: **Fresenius Kabi USA, LLC**, Lake Zurich, IL (US)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 35 days.

(21) Appl. No.: **13/597,884**

(22) Filed: **Aug. 29, 2012**

(65) **Prior Publication Data**

US 2013/0053445 A1 Feb. 28, 2013

**Related U.S. Application Data**

(60) Provisional application No. 61/529,084, filed on Aug. 30, 2011.

(51) **Int. Cl.**

**A61K 31/198** (2006.01)  
**A61K 47/26** (2006.01)  
**A61K 9/00** (2006.01)  
**A61K 9/19** (2006.01)

(52) **U.S. Cl.**

CPC ..... **A61K 9/19** (2013.01); **A61K 9/0019** (2013.01); **A61K 47/26** (2013.01); **A61K 31/198** (2013.01)

(58) **Field of Classification Search**

CPC ... A61K 31/198; A61K 47/26; A61K 9/0019;  
A61K 9/19

See application file for complete search history.

(56) **References Cited**

## U.S. PATENT DOCUMENTS

5,225,204 A \* 7/1993 Chen et al. .... 424/484  
5,955,105 A \* 9/1999 Mitra et al. .... 424/464  
8,318,712 B2 11/2012 Pierres et al.

## FOREIGN PATENT DOCUMENTS

JP 2002284679 10/2002

## OTHER PUBLICATIONS

International Searching Authority, "International Search Report and Written Opinion for PCT/US2012/052838", Nov. 16, 2012, Publisher: European Patent Office, Published in: EP.

Collier, et al., "Influence of Formulation and Processing Factors on Stability of Levothyroxine Sodium Pentahydrate", "APPS PharmSiTech", May 8, 2010, pp. 818-825, vol. 11, No. 2.

Rowe, et al., "Mannitol", "Handbook of Pharmaceutical Excipients", 2006, pp. 449-453.

Searles, JA. "Freezing and Annealing Phenomena in Lyophilization." Freeze Drying/Lyophilization of Pharmaceutical and Biological Products, 3rd Edition. Ed. Louis Rey, Ed. Joan C. May. London: Informa Healthcare, 2010. 52-81.

Won, CM. "Kinetics of Degradation of Levothyroxine in Aqueous Solution and in Solid State," Pharm. Res., 9: 131-137 (1992).

APP Pharmaceuticals, LLC, "Highlights of Prescribing Information", 2011, pp. 1-11.

APP Pharmaceuticals, LLC, "Levothyroxine Sodium for Injection", 2008, pp. 1-3.

Baheti, et al., "Excipients used in lyophilization of small molecules", "J. Excipients and Food Chem.", 2010, pp. 41-54, vol. 1, No. 1.

Bedford Laboratories, "Levothyroxine Sodium for Injection", 2003, pp. 1-2.

Schering Corporation, "Leventa—levothyroxine sodium solution", 2010, pp. 1-3.

Vidyya Medical News Service, "Synthroid, The Most Commonly Prescribed Medication in the US", 2000, pp. 1-11.

Beth D. Herman et al., The Effect of Bulking Agent on the Solid-State Stability of Freeze-Dried Methylprednisolone Sodium Succinate, Pharmaceutical Research, vol. 11, No. 10, pp. 1467-1473 (May 11, 1994).†

Alexandra I. Kim et al., The physical state of mannitol after freeze-drying: effects of mannitol concentration, freezing rate, and a noncrystallizing cosolute, Journal of Pharmaceutical Sciences, vol. 87, No. 8, pp. 931-935 (May 11, 1998).†

\* cited by examiner

*Primary Examiner* — Kara R McMillian

(74) *Attorney, Agent, or Firm* — Blanchard & Associates

(57) **ABSTRACT**

A levothyroxine composition includes levothyroxine sodium and mannitol. The composition is a solid. The composition may include from 100 to 500 micrograms levothyroxine sodium and from 1 to 5 milligrams mannitol. The composition may include from 100 to 200 micrograms levothyroxine sodium, and the mass ratio of mannitol to levothyroxine sodium in the composition may be at most 40:1. The composition may include about 500 micrograms levothyroxine sodium, and the mass ratio of mannitol to levothyroxine sodium in the composition may be at most 10:1.

**21 Claims, 3 Drawing Sheets**